BEST AVAILABLE COPY

0002-9270/94/8902-0267$03.00/0
THE AMERICAN JOURNAL OF GASTROENTEROLOGY
Copyright © 1994 by Am. Coll. of Gastroenterology
Vol. 89, No. 2, 1994
Printed in U.S.A.

Pancreatic Secretion in Man: Effect of Fasting, Drugs, Pancreatic Enzymes, and Somatostatin

Bhupinderjit S. Anand, M.D., D.Phil., Richard Goodgame, M.D., and David Y. Graham, M.D.
Digestive Diseases Section, VA Medical Center and Baylor College of Medicine, Houston, Texas

The inhibitory effect of different drugs on pancreatic secretions was assessed in a patient with a posttraumatic pancreatic-cutaneous fistula. The various drugs examined were: pancreatic enzymes, cimetidine, verapamil, propantheline, acetazolamide, and somatostatin analog octreotide. Only fasting and octreotide reduced pancreatic secretion. The optimum dose of octreotide was 50 μg *bid* given subcutaneously; increasing the dose up to 100 μg *tid* had no additional benefit. A stable pancreatic-cutaneous fistula is an excellent model to assess the effect of different therapeutic measures on pancreatic secretion.

INTRODUCTION

Under physiological conditions, the major stimuli for pancreatic exocrine secretion are food and gastric acid which mediate their response by stimulation of cholinergic neurons and gastrointestinal hormones such as secretin and cholecystokinin (1). Conversely, inhibition of these factors by alkalinization of the duodenum (2) and use of anticholinergic agents (3) and adrenergic agonists (4) reduces pancreatic secretion. Pancreatic enzymes have been shown to inhibit the exocrine secretions of the pancreas (5). Calcium channel blockers have been used since cholecystokinin increases calcium concentration in the acinar cells (6). Acetazolamide has been shown to inhibit pancreatic bicarbonate secretion (7). Finally, the role of somatostatin has been extensively studied (8). However, despite the scientific rationale, these drugs have produced variable results, and the present study was designed to examine their effect under controlled conditions in a patient with a chronic pancreatic-cutaneous fistula.

CASE HISTORY

A 26-yr-old man developed signs of peritonitis following blunt trauma to the abdomen. At laparotomy, pancreatic contusion was observed and a catheter was left in the pancreatic bed which started draining a clear fluid with a high amylase content of >80,000U/ml. An endoscopic retrograde pancreatogram demonstrated a communication between the pancreatic duct and the fistula. The patient was kept fasting and treated with intravenous alimentation for 2 wk. The fistula output decreased to <300 ml/day, but when the feeding was resumed the output increased to >800 ml/day. The patient remained in good health and was discharged with the understanding that if the fistula remained in a steady state for 6 months, surgical correction would be attempted.

Received Mar. 18, 1993; accepted Sept. 20, 1993.

MATERIALS AND METHODS

The fistulous drainage remained steady, and because the output could be accurately measured, we had an opportunity to examine the effect of various drugs in reducing pancreatic secretions. An informed consent was obtained and the Institutional Review Board approved the study.

Experiment 1

These experiments were performed while the patient lived at home and ate an unrestricted diet. The pancreatic fluid drained into an ileostomy bag applied to the abdominal wall. The patient was instructed to empty the bag into a graduated cylinder and record the date, time, and volume. The baseline output was recorded for 13 days. The patient then received the following medications: pancreatic enzymes (three Ilozyme tablets and three pancrease capsules with each meal) on days 14–17; verapamil (80 mg *qid*) on days 21–26, and cimetidine (300 mg *qid*) on days 28–32.

Experiment 2

The patient was hospitalized and received the same meals at about the same time each day. The total daily intake was 2800 calories, composed of 241 g carbohydrate, 148 g protein, and 169 g fat. At 8 AM each day the bag was emptied and a 10-h study period was initiated; the bag was emptied every 2 h and the volume recorded. Five-milliliter samples were taken during the first 4 h and over the last 6 h to measure the protein content. A total of seven, 10-h study periods were performed on consecutive days. The first, third, and

BEST AVAILABLE COPY

fifth days served as control periods when no drug was administered. The second day was used to study the effect of 300 mg cimetidine administered *p.o.* at 10 PM the night before, and at 6 AM, 10 AM, and 2 PM the next day. The fourth day was used to test the effect of propantheline, 30 mg orally at 10 PM the night before and at 6 AM, 10 AM, and 2 PM. On the sixth day, 80 mg verapamil was given *p.o.* at 10 PM the night before and at 6 AM, 10 AM, and 2 PM. On the seventh day, the patient fasted during the entire study period; protein analysis of the pancreatic fluid was not performed. The final experiment consisted of obtaining six consecutive 24-h fistula collections. During the first 24 h, the patient took no medications; the next 5 days the patient received acetazolamide, 500 mg *qid*. The fluid output and protein content of each 24-h collection was measured.

Experiment 3

The patient was admitted to the General Clinic Research Center. These experiments were designed to examine the effect of octreotide (Sandostatin, Sandoz, East Hanover, NJ), and to determine its optimum dose. The patient was placed on a 2950 isocaloric diet and pancreatic enzymes (Ilozyme, four tablets with each meal) throughout the study period. The baseline output was recorded for the first 3 days. On day 4, 50 μg octreotide were given subcutaneously (SQ) *bid*. After 2 days (day 6), the dose was increased to 100 μg *bid*, and after 4 days (day 10), was further increased to 100 μg *tid*. Two days later, acetazolamide 250 mg *qid* was added to the treatment for 1 day. On day 13, both octreotide and acetazolamide were stopped and the output was recorded for 2 days before the study was terminated.

RESULTS

The results of experiment 1 are shown in Figure 1. The mean (±SD) baseline output over the first 13 days was 915 (±194) ml/day. There was no appreciable change in the fistula output after treatment with pancreatic enzymes (935 ± 214 ml/day), verapamil (932 ± 236 ml/day), and cimetidine (885 ± 162 ml/day).

The results of experiment 2 are shown in Figure 2. There was no significant difference in the output during the control period (mean ± SD of three 10-h periods = 336 ± 58 ml) compared with the output following use of cimetidine (378 ml), probanthine (405 ml), and verapamil (380 ml). On day 7, when the patient fasted the entire day, there was a sharp drop in the output to 58 ml. Resumption of normal diet was followed by an increase in output to 550 ml over the next 24 h. There was no decrease in the fistula output with acetazolamide (mean ± SD = 541 ± 170 ml/day). There was no appreciable difference in the protein content of the fluid collected during the control period (880 ± 180

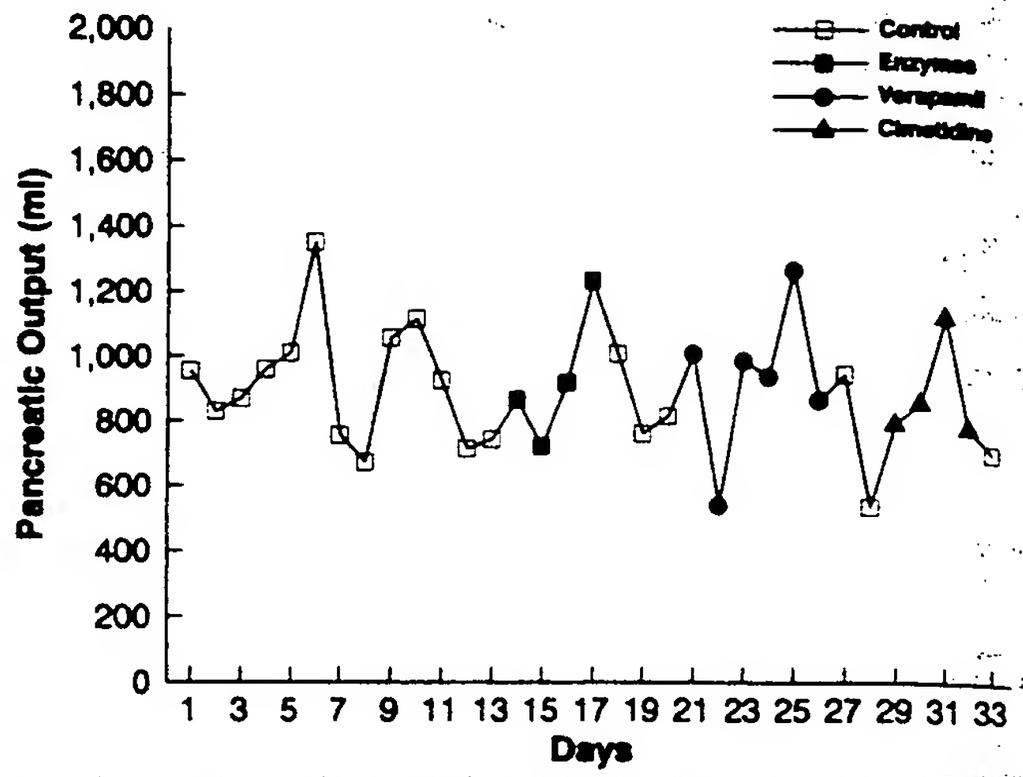

FIG. 1. Daily output from the pancreatic-cutaneous fistula during the first 13 days of baseline collection and after treatment with pancreatic enzymes, verapamil, and cimetidine. None of the drugs had an appreciable inhibitory effect on the fistula output.

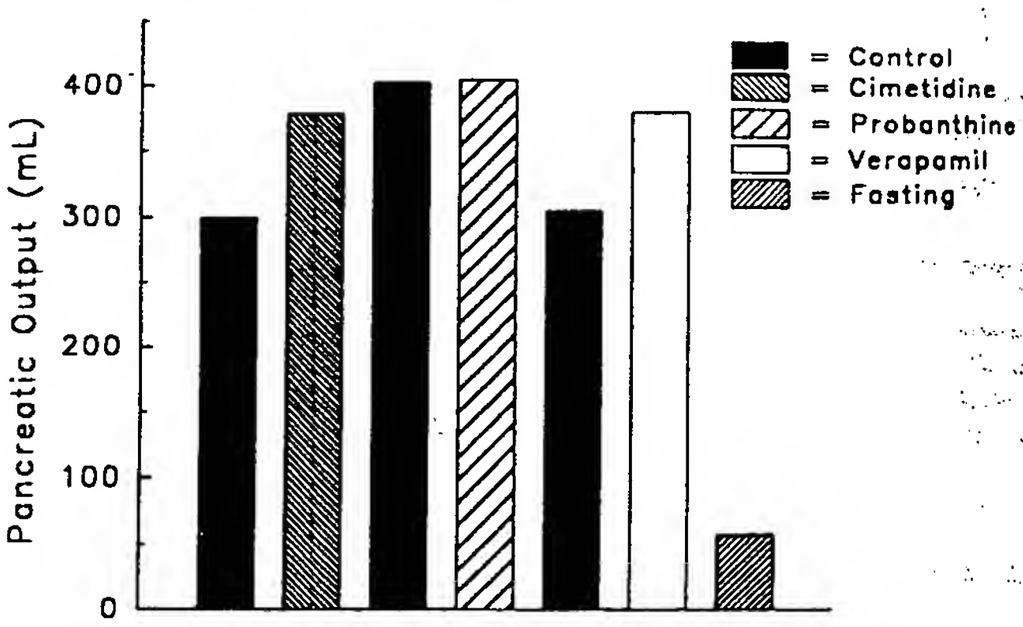

FIG. 2. Fistula output over 10-h collection periods each day during the control study and after treatment with cimetidine, probanthine, verapamil, and during fasting. None of the drugs produced any inhibition of pancreatic secretion. However, fasting resulted in an appreciable fall in the fistula output.

mg/day) and after cimetidine (850 mg/day), probanthine (1100 mg/day), and verapamil (650 mg/day).

The results of experiment 3 are shown in Figure 3. The fluid volume over the 3-day control period was 435 ± 33.5 ml/day. Octreotide, 50 μg *bid*, produced a marked fall in the output (173 ± 21.2 ml/day). An increase in the dose of octreotide to 100 μg *bid* and then to 100 μg *tid* did not further decrease the output (165.2 ± 5.1 and 182.5 ± 23.3 ml/day, respectively). The addition of acetazolamide, 250 mg *qid*, to octreotide (100 μg *tid*) had no further inhibitory effect (154 ml/day). Cessation of octreotide therapy resulted in prompt increase in the output; mean (±SD) of 2-day values was 376 (±80.1) ml/day. No adverse effect was observed with any of the drugs.

DISCUSSION

A logical assessment of the physiological stimuli of the pancreas suggests that a number of drugs such as

BEST AVAILABLE COPY

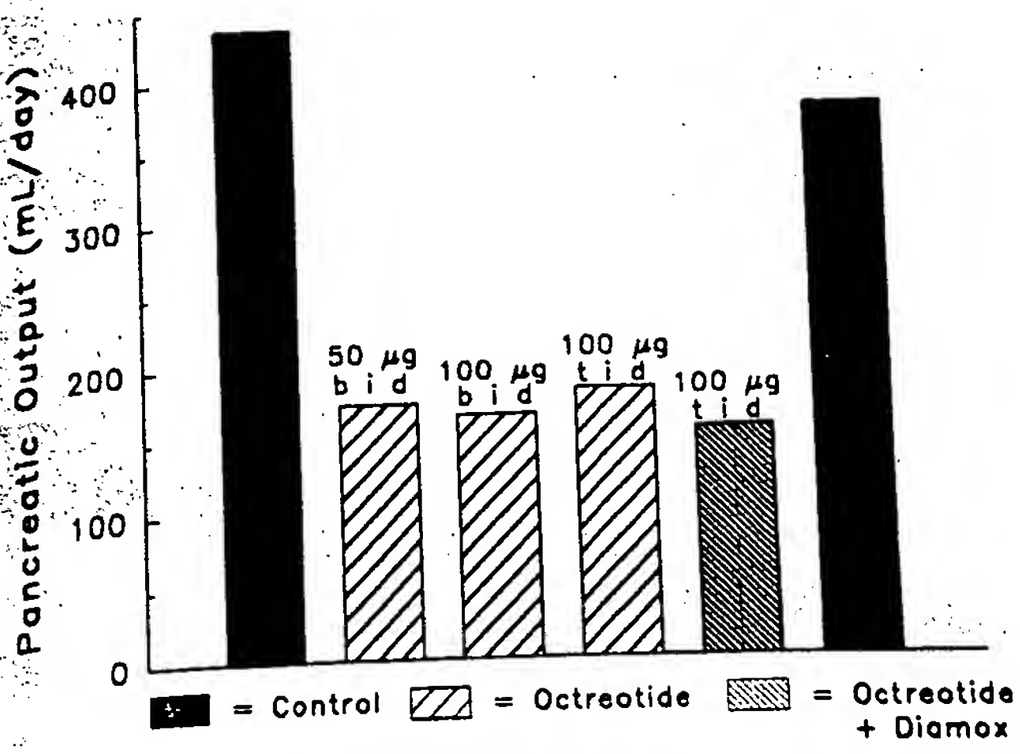

FIG. 3. Fistula output during each 24-h study period. Octreotide produced a marked fall in the fistula output. The optimum effect was produced by 50 µg *bid*, and no additional benefit was obtained by increasing the dose of octreotide to 100 µg *tid* or by the addition of Diamox.

probanthine, cimetidine, verapamil, pancreatic enzymes, acetazolamide, and octreotide should reduce pancreatic secretions. However, few of these agents have been assessed in a scientific manner. The present patient with a stable pancreatic-cutaneous fistula provided us with an opportunity to examine these drugs under controlled conditions. Such a study is important, as it can help determine the role of various drugs in disorders requiring suppression of pancreatic secretion. Pancreatic fistulas are arbitrarily divided into low output (<200 ml/day) and high output fistulas (>200 ml/day). According to this definition, our patient had the high output variety.

The present study was carried out in three parts. The first set of experiments were carried out while the patient was at home. Although the patient's compliance with the study protocol was good, he had variable eating habits, both in the timing of his meals and in the quantity of food eaten. The variability in the time at which the patient emptied the contents of the bag was reduced by assessing the mean output per day. In the experiments carried out at the hospital, the patient was fed isocaloric meals at the same time every day and the fluid output was carefully recorded.

Fasting alone decreased the fistula output from an average of >300 ml over the 10-h study period to 58 ml. This observation is in agreement with the encouraging results obtained with total parenteral nutrition (9), and is perhaps related to the lack of meal-induced pancreatic stimulation. However, total parenteral nutrition alone is often unsuccessful in closing a pancreatic fistula, and other methods of suppressing pancreatic secretion are required.

A close association between duodenal acidification and pancreatic secretion has been demonstrated (2). However, the effectiveness of reducing acid secretion has not been clearly demonstrated. To examine this, cimetidine was used in a dose of 300 mg *qid*. At this dose, cimetidine maintains the duodenal pH above four in most patients 90% of the time. However, there was no increase in the fistula output or its protein content. We did not measure the patient's baseline acid secretory status or its response to cimetidine treatment, but have no reason to suspect any abnormality in the acid-lowering effect of the drug in this patient.

Pancreatic secretion is a calcium-dependent process (6), and secretagogues such as cholecystokinin and acetylcholine combine with specific membrane receptors, inducing a rise in intracytoplasmic calcium (10). However, in a study on normal volunteers, verapamil had no effect on the basal and stimulated pancreatic secretions (11), and in the present study also, verapamil failed to suppress the fistula output.

Somatostatin has an inhibitory effect on pancreatic secretions irrespective of whether the pancreas is stimulated by meals (12) or by cholecystokinin (13). Somatostatin has a short half-life of <3 min (14) whereas its analog, octreotide, which retains all the biologic effects of somatostatin, acts for 6–12 hr after SQ administration (15). The optimum dose of octreotide has not been determined, and doses varying from 50 µg *bid SQ* to 250 µg/h by *iv* infusion have been used (9, 16). In the present study, the optimum dose of octreotide was 50 µg *bid SQ*; a further increase in the dose to 100 µg *tid* had no additional inhibitory effect.

Some workers have observed feedback inhibition of the pancreas by the use of pancreatic enzymes (5). However, other workers have found no inhibition of the pancreatic secretory output; indeed, even stimulation of the pancreatic secretions has been observed (17, 18). In the present study, pancreatic enzymes had no inhibitory (or stimulatory) effect on pancreatic secretions. Analysis of different studies indicates that anticholinergics reduce pancreatic fistula output by 30–60%; both parenteral atropine and oral probanthine are equally effective (3). Similarly, the carbonic enhydrase inhibitor, acetazolamide, reduces pancreatic secretions (19). However, some workers have found anticholinergics (20) and acetazolamide ineffective (3) in reducing pancreatic secretion. In our patient, probanthine did not reduce either the volume or protein content of the fistula output. Similarly, acetazolamide failed to decrease the fistula output when the drug was given alone and had no additive effect when it was administered with octreotide.

In conclusion, the present study shows that a number of drugs such as pancreatic enzymes, cimetidine, verapamil, probanthine, and acetazolamide when tested under controlled conditions had no inhibitory effect on pancreatic fluid or protein output. This lack of effect

BEST AVAILABLE COPY

may be related to the fact that our patient had a high output (>200 ml/day) fistula which is generally more resistant to treatment. However, the complete absence of any effect argues against such a possibility. Only fasting and octreotide reduced pancreatic secretions. A dose response study with octreotide showed that the optimum dose is 50 μg *bid*. A stable external pancreatic fistula is an excellent experimental model for the assessment of newer therapeutic modalities designed to reduce pancreatic secretion.

Reprint requests and correspondence: B. S. Anand, M.D., Gastroenterology Section, Baylor College of Medicine, Smith Tower, 6550 Fannin, Sm 1101, Houston, TX 77030.

REFERENCES

1. Solomon TE. Regulation of pancreatic secretion. Clin Gastroenterol 1984;13:657–78.
2. Grossman MI, Konturek SJ. Gastric acid does drive pancreatic bicarbonate secretion. Scand J Gastroenterol 1974;9:299–302.
3. Baker RJ, Bass RT, Zajtchuk R, et al. External pancreatic fistula following abdominal injury. Arch Surg 1967;95:556–66.
4. Joehl RJ, Nahrwold DL. Inhibition of human pancreatic secretion by terbutaline as a potential agent for treating patients with pancreatic fistula. Surg Gynecol Obstet 1985;160:109–14.
5. Slaff J, Jacobson D, Tillman CR, et al. Protease-specific suppression of pancreatic exocrine secretion. Gastroenterology 1984;87:44–51.
6. Williams JA. Regulation of pancreatic acinar cell function by intracellular calcium. Am J Physiol 1980;238:G269–G279.
7. Papastrat CJ, Miller JM. Treatment of external pancreatic fistula with Diamox. Am J Dig Dis 1958;3:339–407.
8. Lin TM, Evans DC, Shaar CJ, et al. Action of somatostatin on stomach, pancreas, gastric mucosal blood flow and hormones. Am J Physiol 1983;244:G40–G45.
9. Pederzoli P, Bassi C, Falconi M, et al. Conservative treatment of external pancreatic fistulas with parenteral nutrition alone or in combination with continuous intravenous infusion of somatostatin, glucagon or calcitonin. Surg Gynecol Obstet 1986;163:428–32.
10. Gardner JC, Conlon TP, Klaeveman HL, et al. Action of cholecystokinin and cholenergic agents on calcium transport in isolated pancreatic acinar cells. J Clin Invest 1975;56:366–75.
11. Niederau C, Hellman A, Sonnenberg A, et al. The effects of verapamil on exocrine pancreatic secretion in man. Dig Dis Sci 1985;30:72–7.
12. Johannsson C, Killberg B, Efendic S, et al. Effects of graded doses of somatostatin on gallbladder emptying and pancreatic enzyme output after oral glucose in man. Digestion 1981;22:24–31.
13. Miller TA, Tepperman FS, Fang WF, et al. Effect of somatostatin on pancreatic protein secretion induced by cholecystokinin. J Surg Res 1979;26:488–93.
14. Sheppard MC, Shapiro B, Pimstone BL, et al. Metabolic clearance and plasma half life disappearance time of exogenous somatostatin in man. J Clin Endocrinol Metab 1979;48:50–3.
15. Lembcke B, Creutzfeldt W, Schleser S, et al. Effect of the somatostatin analogue sandostatin (SMS 201–995) on gastrointestinal, pancreatic and biliary function and hormone release in normal man. Digestion 1987;36:108–24.
16. Ahren B, Tranberg KG, Bengmark S. Treatment of pancreatic fistula with the somatostatin analogue SMS 201–995. Br J Surg 1988;75:718.
17. Mossner J, Wresky H-P, Kestel W, et al. Influence of treatment with pancreatic enzymes on pancreatic enzyme secretion. Gut 1989;30:1143–9.
18. Mossner J, Stange JH, Ewald M, et al. Influence of exogenous application of pancreatic extracts on endogenous pancreatic enzyme secretion. Pancreas 1991;6:637–44.
19. Pak BH, Hong SS, Pak HK, et al. Effects of acetazolamide and acid-base changes on biliary and pancreatic secretion. Am J Physiol 1966;210:624–8.
20. Anderson MC, Mehn WH; Method HL. Physiologic observations upon a partial pancreatic fistula following gastrectomy. Am J Surg 1959;97:260–9.